P[illegible]ENT COOPERATION TREA[illegible]

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 June 2000 (21.06.00)	
International application No. PCT/US99/25365	**Applicant's or agent's file reference** 19603/2593
International filing date (day/month/year) 28 October 1999 (28.10.99)	**Priority date** (day/month/year) 28 October 1998 (28.10.98)
Applicant HEMPSTEAD, Barbara, L. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 May 2000 (24.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer I. Britel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US9925365

EXPRESS MAIL CERTIFICATE

DOCKET NO.: 19603/2595

APPLICANT(S): HEMPSTEAD et al.

TITLE: METHODS FOR REGULATING ANGIOGENESIS AND VASCULAR INTEGRITY USING TRK RECEPTOR LIGANDS

Certificate is attached to the Copy of the Preliminary Examination Report of the above-named application.

"EXPRESS MAIL" NUMBER: EL710757195US

DATE OF DEPOSIT: April 26, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Box PCT, Washington, D.C. 20231.

Wendy L. Harrold
(Typed or printed name of person mailing paper or fee)

Wendy L. Harrold
(Signature of person mailing paper **or** fee)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GOLDMAN, Michael L.
Nixon Peabody LLP
Clinton Square
P.O. Box 1051
Rochester, NY 14603
ETATS-UNIS D'AMERIQUE

ENTERED
Nixon Peabody LLP
MAR 1 4 2001
FILE 19603/2593
DKT

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 05.03.2001
Applicant's or agent's file reference 19603/2593	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/25365	28/10/1999	28/10/1998

Applicant
CORNELL RESEARCH FOUNDATION, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
19603/2593		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/25365	28/10/1999	28/10/1998
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant CORNELL RESEARCH FOUNDATION, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/05/2000	05.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Perez. F Telephone No. +49 89 2399 7338

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25365

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-37 as originally filed

Claims, No.:

1-54 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-46 (IA).

because:

☒ the said international application, or the said claims Nos. 1-46 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30, 35-36, 38-39, 44-45, 47-48, 49-54
	No:	Claims	31-34, 37, 40-43, 46
Inventive step (IS)	Yes:	Claims	12-13
	No:	Claims	1-11, 14-54
Industrial applicability (IA)	Yes:	Claims	47-54 (for 1-46 see separate sheet)
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II

Priority

The priority date claimed has been found invalid for part of the subject-matter of the present application. Nevertheless, P-documents D12 and D13 relate to subject-matter covered by the priority document dated of 28 october 1998. Therefore they do not constitute prior art for the purpose of Article 33.2 and 33.3 (Rule 64.1 PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34.4(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: OIKAWA T ET AL. JOURNAL OF ANTIBIOTICS, vol. 45, no. 7, July 1992, pages 1155-1160.
D2: HARDIE G & HANKS S (EDS.), 1995 , ACADEMIC PRESS , LONDON
D3: US-A-5 654 427 (MURAKATA CHIKARA ET AL) 5 August 1997.
D4: WO 95 21193 A (UNIV MCGILL ;SARAGOVI URI H (CA); LESAUTEUR LYNNE (CA); CUELLO A C) 10 August 1995.
D5: WO 97 21732 A (UNIV MCGILL ;SARAGOVI H URI (CA); LESAUTEUR LYNNE (CA)) 19 June 1997.
D6: WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000.
D7: WO 96 33731 A (REGENERON PHARMA) 31 October 1996.
D8: US-A-5 817 471 (PARADA LUIS F ET AL) 6 October 1998.
D9: WO 98 32859 A (CORNELL RES FOUNDATION INC ;CRYSTAL RONALD G (US); ROSENGART TODD) 30 July 1998.

D10: HEMPSTEAD B L. EXPERIMENTAL NEUROLOGY, vol. 124, no. 1, November 1993, pages 31-35.
D11: DONOVAN MJ ET AL. AMERICAN JOURNAL OF PATHOLOGY, vol. 147, no. 2, August 1995, pages 309-324.
D12: HEMSPTEAD B ET AL. BLOOD, vol. 92, no. 10 SUPPL. 1 PART 1-2, 15 November 1998, page 175A.
D13: MCGREGOR LM ET AL. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 96, no. 8, 13 April 1999, pages 4540-4545.

Document D12 and D13 are P-documents. Document D7 is a E-document.

Novelty (Articles 33.1 and 33.2 PCT)

The use of a trk receptor ligand for treating pathological disorders is known from the prior art, (see D4 column 2, line 5-18; D5 claims 3-4, 14; D6 claim 3; D9 claim 3; D10 column 12, line 30-33). Nevertheless none of those disorders are treated by inducing angiogenesis or by promoting vessel growth or stabilisation. Therefore **claims 1-30** are novel.

Claims 31-46 relate to methods of inhibiting angiogenesis by delivering an inhibitor of the expression of trk receptor ligand. Document D1 discloses the inhibition of angiogenesis by staurosporin which is a trkA receptor ligand (as confirmed by D3). The use of small molecules or antibodies binding to trk A, B or C receptors for treatment of cancer (this disease falls within the scope of claim 31) is known (D4, column 2 line 5-21; D5, claim 15, page 9 line 18-19; D6, claim 5). Therefore **claims 31-34, 37, 40-43, 46**, as far as they implicitely or explicitely cover a method of treating cancer using a trk ligand, lack novelty. The use of a trk receptor body or antisense molecule as inhibitors of trk receptor ligands activity for inhibiting angiogenesis, or the use of any inhibitors of trk receptor ligands activity for treating the diseases specified in claims 38-39, are not disclosed in the prior art. Therefore **claims 35-36, 38-39, 44-45** are novel.

Claims 47-48 relate to method of screening compounds modulating angiogenesis, vessel growth or vessel stabilisation. D6 discloses a method of screening compound which bind to trkA receptor and are suitable for treating cancer (claims 5-6, 9). Nevertheless the steps involved in the screenings are different, e.g. detection of signal transduction in the

application and detection of binding to an antibody for D6. Therefore **claim 47-48** are novel.

Claim 49 (interpreted as indicated in item VIII below) relates to a method of diagnosing or monitoring a pathological disorder selected in the group consisting of the diseases enumerated in claim 54 by determining the presence or the amount of a trk receptor ligand in a biological sample or the activation of a trk receptor. Whereas similar technic is known for the monitoring of neurodegenerative diseases (see D10 summary of the invention), the diagnostic or monitoring of said diseases in not disclosed in the priort art. Therefore **claim 49** and subsequent dependant **claims 50-54** are novel.

Inventive Step (Articles 33.1 and 33.3 PCT)

The present application is based on the finding that trk receptor can modulate angiogenesis, particularly by promoting vessel growth or stabilisation. This application presents various aspects related to this finding, namely methods of screening compounds modulating angiogenesis, methods of treating, diagnosing and monitoring diseases that can be treated by modulating angiogenesis or related biological events such as vessel growth or stabilisation.

None of the cited prior art does suggest the ability of trk receptor to modulate angiogenesis.

However, D8 teaches that activation of trk receptors in vivo could stimulate vascular smooth muscle cells migration in the artery wall (page 321 "Regulation of ligand and receptor expression"), thus stabilising vessels. It would be a matter of routine for the skilled man to derive the subject-matter of claims 20-30, 47-54 from this teaching of D8. Therefore subject-matter of **claims 20-30, 47-54**, for those parts covering vessel stabilization by trk receptors, cannot be considered as inventive.

Moreover, D8 also suggest that neurotrophins play an important role in regulating the response to vascular injury (wound). It would be a matter of routine for the skilled man to derive the subject-matter of claims 11(completely) and 1-10, 14-19 (for the part related to the treatment of wound) from this suggestion of D8. Therefore the subject-matter of **claims 1-11, 14-19,** for those parts explicitly or implicitly covering wound treatment,

cannot be considered as inventive.

Similarly, the treatment of cancer with trk receptors ligands is known (e.g. D4, column 2 line 5-21; D5, claim 15, page 9 line 18-19; D6, claim 5). It would be a matter of routine for the skilled man to derive the subject-matter of claims 31-46, 47-54 for the part related to the treatment of cancer from said prior art. Therefore the subject-matter of **claims 31-46, 47-54,** for those parts which explicitly or implicitly cover cancer treatment, cannot be considered as inventive.

For those claims not anticipated or obvious from the priort art, an inventive step can be acknowledged as the prior art does not generally teach that trk receptor can modulate angiogenesis.

Industrial applicability (Articles 33.1 and 33.4 PCT)

For the assessment of the present **claims 1-46** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 49-54 relate to *in vitro* methods of diagnostic and are therefore succeptible of industrial application.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10 PCT)

Application No WO/00/10552

Re Item VIII
Certain observations on the international application

Claims 7, 20, 26 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT). The same objection apply for **claim 37** with regard to claim 31.

The term "activation of trk receptor ligand" used in claim 49 is unclear. The description (page 19, line 31-page 20, line 2) when refering to said term, read "In one embodiement, the determining (of activation of a trk receptor ligand) comprises assessing trk tyrosine phosphorylation, as described above". In contradiction, above citation of the description (page 19, line 8-16) make reference to a test for assessing activation of trk receptor rather than trk receptor ligand. Therefore it is unclear if "trk receptor activation" or "trk receptor ligand activation" is meant. Therefore, **claim 49** lacks clarity (Article 6 PCT). For the purpose of this report, the term "activation of trk receptor ligand" as been interpreted as "activation of trk receptor".

Claim 49 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. The reason is that subject-matter of claim 49 covers method for diagnosing or monitoring any pathological disorder, whereas only the diagnosis or monitoring of a limited number of diseases is supported by the description. For the purpose of this report, the term "a pathological disorder" has been interpreted as the conditions enumerated in claim 54.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
19603/2593		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/25365	28/10/1999	28/10/1998
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant CORNELL RESEARCH FOUNDATION, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/05/2000	05.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Perez, F Telephone No. +49 89 2399 7338

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25365

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-37 as originally filed

Claims, No.:

1-54 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-46 (IA).

because:

☒ the said international application, or the said claims Nos. 1-46 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30, 35-36, 38-39, 44-45, 47-48, 49-54
	No:	Claims	31-34, 37, 40-43, 46
Inventive step (IS)	Yes:	Claims	12-13
	No:	Claims	1-11, 14-54
Industrial applicability (IA)	Yes:	Claims	47-54 (for 1-46 see separate sheet)
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II

Priority

The priority date claimed has been found invalid for part of the subject-matter of the present application. Nevertheless, P-documents D12 and D13 relate to subject-matter covered by the priority document dated of 28 october 1998. Therefore they do not constitute prior art for the purpose of Article 33.2 and 33.3 (Rule 64.1 PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34.4(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: OIKAWA T ET AL. JOURNAL OF ANTIBIOTICS, vol. 45, no. 7, July 1992, pages 1155-1160.
D2: HARDIE G & HANKS S (EDS.), 1995 , ACADEMIC PRESS , LONDON
D3: US-A-5 654 427 (MURAKATA CHIKARA ET AL) 5 August 1997.
D4: WO 95 21193 A (UNIV MCGILL ;SARAGOVI URI H (CA); LESAUTEUR LYNNE (CA); CUELLO A C) 10 August 1995.
D5: WO 97 21732 A (UNIV MCGILL ;SARAGOVI H URI (CA); LESAUTEUR LYNNE (CA)) 19 June 1997.
D6: WO 00 10552 A (GLOBAL VASCULAR CONCEPTS INC) 2 March 2000.
D7: WO 96 33731 A (REGENERON PHARMA) 31 October 1996.
D8: US-A-5 817 471 (PARADA LUIS F ET AL) 6 October 1998.
D9: WO 98 32859 A (CORNELL RES FOUNDATION INC ;CRYSTAL RONALD G (US); ROSENGART TODD) 30 July 1998.

D10: HEMPSTEAD B L. EXPERIMENTAL NEUROLOGY, vol. 124, no. 1, November 1993, pages 31-35.
D11: DONOVAN MJ ET AL. AMERICAN JOURNAL OF PATHOLOGY, vol. 147, no. 2, August 1995, pages 309-324.
D12: HEMSPTEAD B ET AL. BLOOD, vol. 92, no. 10 SUPPL. 1 PART 1-2, 15 November 1998, page 175A.
D13: MCGREGOR LM ET AL. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 96, no. 8, 13 April 1999, pages 4540-4545.

Document D12 and D13 are P-documents. Document D7 is a E-document.

Novelty (Articles 33.1 and 33.2 PCT)

The use of a trk receptor ligand for treating pathological disorders is known from the prior art, (see D4 column 2, line 5-18; D5 claims 3-4, 14; D6 claim 3; D9 claim 3; D10 column 12, line 30-33). Nevertheless none of those disorders are treated by inducing angiogenesis or by promoting vessel growth or stabilisation. Therefore **claims 1-30** are novel.

Claims 31-46 relate to methods of inhibiting angiogenesis by delivering an inhibitor of the expression of trk receptor ligand. Document D1 discloses the inhibition of angiogenesis by staurosporin which is a trkA receptor ligand (as confirmed by D3). The use of small molecules or antibodies binding to trk A, B or C receptors for treatment of cancer (this disease falls within the scope of claim 31) is known (D4, column 2 line 5-21; D5, claim 15, page 9 line 18-19; D6, claim 5). Therefore **claims 31-34, 37, 40-43, 46**, as far as they implicitely or explicitely cover a method of treating cancer using a trk ligand, lack novelty. The use of a trk receptor body or antisense molecule as inhibitors of trk receptor ligands activity for inhibiting angiogenesis, or the use of any inhibitors of trk receptor ligands activity for treating the diseases specified in claims 38-39, are not disclosed in the prior art. Therefore **claims 35-36, 38-39, 44-45** are novel.

Claims 47-48 relate to method of screening compounds modulating angiogenesis, vessel growth or vessel stabilisation. D6 discloses a method of screening compound which bind to trkA receptor and are suitable for treating cancer (claims 5-6, 9). Nevertheless the steps involved in the screenings are different, e.g. detection of signal transduction in the

application and detection of binding to an antibody for D6. Therefore **claim 47-48** are novel.

Claim 49 (interpreted as indicated in item VIII below) relates to a method of diagnosing or monitoring a pathological disorder selected in the group consisting of the diseases enumerated in claim 54 by determining the presence or the amount of a trk receptor ligand in a biological sample or the activation of a trk receptor. Whereas similar technic is known for the monitoring of neurodegenerative diseases (see D10 summary of the invention), the diagnostic or monitoring of said diseases in not disclosed in the priort art. Therefore **claim 49** and subsequent dependant **claims 50-54** are novel.

Inventive Step (Articles 33.1 and 33.3 PCT)

The present application is based on the finding that trk receptor can modulate angiogenesis, particularly by promoting vessel growth or stabilisation. This application presents various aspects related to this finding, namely methods of screening compounds modulating angiogenesis, methods of treating, diagnosing and monitoring diseases that can be treated by modulating angiogenesis or related biological events such as vessel growth or stabilisation.

None of the cited prior art does suggest the ability of trk receptor to modulate angiogenesis.

However, D8 teaches that activation of trk receptors in vivo could stimulate vascular smooth muscle cells migration in the artery wall (page 321 "Regulation of ligand and receptor expression"), thus stabilising vessels. It would be a matter of routine for the skilled man to derive the subject-matter of claims 20-30, 47-54 from this teaching of D8. Therefore subject-matter of **claims 20-30, 47-54**, for those parts covering vessel stabilization by trk receptors, cannot be considered as inventive.

Moreover, D8 also suggest that neurotrophins play an important role in regulating the response to vascular injury (wound). It would be a matter of routine for the skilled man to derive the subject-matter of claims 11(completely) and 1-10, 14-19 (for the part related to the treatment of wound) from this suggestion of D8. Therefore the subject-matter of **claims 1-11, 14-19,** for those parts explicitly or implicitly covering wound treatment,

cannot be considered as inventive.

Similarly, the treatment of cancer with trk receptors ligands is known (e.g. D4, column 2 line 5-21; D5, claim 15, page 9 line 18-19; D6, claim 5). It would be a matter of routine for the skilled man to derive the subject-matter of claims 31-46, 47-54 for the part related to the treatment of cancer from said prior art. Therefore the subject-matter of **claims 31-46, 47-54,** for those parts which explicitly or implicitly cover cancer treatment, cannot be considered as inventive.

For those claims not anticipated or obvious from the priort art, an inventive step can be acknowledged as the prior art does not generally teach that trk receptor can modulate angiogenesis.

Industrial applicability (Articles 33.1 and 33.4 PCT)

For the assessment of the present **claims 1-46** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 49-54 relate to *in vitro* methods of diagnostic and are therefore succeptible of industrial application.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10 PCT)

Application No WO/00/10552

Re Item VIII
Certain observations on the international application

Claims 7, 20, 26 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT). The same objection apply for **claim 37** with regard to claim 31.

The term "activation of trk receptor ligand" used in claim 49 is unclear. The description (page 19, line 31-page 20, line 2) when refering to said term, read "In one embodiement, the determining (of activation of a trk receptor ligand) comprises assessing trk tyrosine phosphorylation, as described above". In contradiction, above citation of the description (page 19, line 8-16) make reference to a test for assessing activation of trk receptor rather than trk receptor ligand. Therefore it is unclear if "trk receptor activation" or "trk receptor ligand activation" is meant. Therefore, **claim 49** lacks clarity (Article 6 PCT). For the purpose of this report, the term "activation of trk receptor ligand" as been interpreted as "activation of trk receptor".

Claim 49 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and drawings. The reason is that subject-matter of claim 49 covers method for diagnosing or monitoring any pathological disorder, whereas only the diagnosis or monitoring of a limited number of diseases is supported by the description. For the purpose of this report, the term "a pathological disorder" has been interpreted as the conditions enumerated in claim 54.